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(54) **NITRIC ESTERS HAVING ANTI-INFLAMMATORY AND/OR ANALGESIC ACTIVITY AND PROCESS FOR THEIR PREPARATION**

SALZETERSAÜREESTER MIT ENTZÜNDUNGSHEMMENDER UND/ODER SCHMERZLINDERNDER WIRKUNG UND VERFAHREN ZU DEREN HERSTELLUNG

ESTERS NITRIQUES DOTES D'UNE ACTIVITE ANTI-INFLAMMATOIRE ET/OU ANALGESIQUE ET LEUR PROCEDE DE PREPARATION

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US-A- 3 758 544

EP 0 722 434 B1

Description

OBJECT OF THE INVENTION

The present invention refers to nitric esters of derivatives of propionic acid, 1-(p-chlorobenzoyl)-5-methoxy-2-methyl -3-indolylacetic acid, 5-benzoyl -1,2-dihidro -3H- pyrrolo[1,2-a]pyrrole -1-carboxylic acid, 6-methoxy -2-naphthylacetic acid, their pharmaceutical utilization and the process for their preparation. The present invention also refers to pharmaceutical compositions comprising at least one of said nitric esters as active constituent.

PRIOR ART

Some derivatives of propionic acid, such as, for instance, 2-(6-methoxy-2-naphtyl)propionic acid 2-(4-isobutylphenyl)propionic acid or alpha-Methyl-4-[(2-oxocyclopentyl)methyl]benzeneacetic acid, have been used for a long time in the pharmaceutical field for their anti-inflammatory activity and have been present for many years on the different world markets. The process for the preparation of 2-(6-methoxy-2-naphtyl)propionic acid has been described in the South African Patent N°6707,597, in the German Patent N° 1,934,460, corresponding to the US Patent N°3,637,767 and also in C.A.71,91162] (1969); HARRISON et al. J.Med.Chem. 13,203 (1970); the process for the preparation of 2-(4-isobutylphenyl)propionic acid has been described in Patents GB N°971,700, US N°3,228,831 and US N°3,385,886, and also in T. SHIORI, N. KAWAI, J.Org. Chem. 43,2936 (1978); J.T. PINHEY, B.A. ROWE, Tetrahedron Letters 21, 965 (1980);while the process for the preparation of alpha-methyl-4-[(2-oxocyclopentyl)methyl]benzenacetic acid has been described in the German Patent N°2,814,556 and in US Patent N°4,161,538.

In the case of 2-(6-methoxy-2-naphtyl)propionic acid, the pharmacological profile is described in ROSZKOWSKI et al. J. Pharmacol. Exp. Ther. 179,114 (1971), while the pharmacological profile of 2-(4-isobutylphenyl)propionic acid is reported in ADAMS et al. Arch. Pharmacodyn. Ther. 178,115 (1969).

The utilization of these derivatives of propionic acid as anti-inflammatory agents involves, as known, extremely severe adverse reactions affecting, for instance, the gastrointestinal system, as well as damages to liver and kidneys.

WO-A-94/04484 discloses nitric esters of derivatives of the 2-(2,6-di-halophenylamino)phenylacetic acid, a process for their preparation and their pharmaceutical utilization.

Other particularly toxic products are, for example, 5-benzoyl -,2- dihydro-3H- pyrrolo[1,2-a] pyrrole 1-carboxylic acid or Ketorolac [W.H.ROOKS et al. Agents Actions 12,684 (1982)] and 1-(4-chlorobenzoyl)-5-methoxy-2- methyl- 1H-indole- 3-acetic acid or Indomethacin [C.D.KLAASSEN, Toxicol. Appl.Pharmacol. 28,127 (1976)]. In particular, in some countries Ketorolac has been withdrawn from the market because of its gastrointestinal toxicity, while Indomethacin is one of the drugs which has caused the highest death-rate from the year of its introduction in the market. Compared with other known anti-inflammatory and/or analgesic drugs, Ketorolac and Indomethacin cause - because of the already described adverse reactions - very extensive damages and, in particular as concerns gastrointestinal toxicity, deaths have been ascertained even in children.

It is therefore evident that there is the need of having drugs which, though providing a good anti-inflammatory and/or analgesic activity, do not result to be, in general, toxic.

OBJECTS OF THE INVENTION

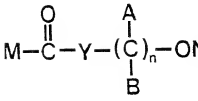
Object of the present invention is that of providing a product which, while assuring at least the maintenance of the pharmacological activity which is characteristic of the known anti-inflammatory and/or analgesic agents, is capable of eliminating the adverse reactions brought about by the treatment with said agents, and has good tolerance.

Another object of the present invention is that of realizing a process for the preparation of derivatives of propionic acid, 1-(p-chlorobenzoyl)-5- methoxy-2-methyl -3-indolylacetic acid, 5-benzoyl -1,2-dihidro -3H- pyrrolo[1,2-a]pyrrole -1-carboxylic acid, 6-methoxy -2-naphthylacetic acid, having an anti-inflammatory and/or analgesic activity, good tolerance and being exempt from the adverse reactions that are typical of anti-inflammatory and analgesic agents.

Still another object of the present invention is that of providing pharmaceutical compositions having anti-inflammatory and/or analgesic activity which results provided with good tolerance.

DESCRIPTION OF THE INVENTION

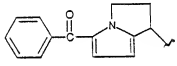
These and still further objects and associated advantages which shall clearly result from the following description, are reached by derivatives of propionic acid, 1-(p-chlorobenzoyl)-5- methoxy-2-methyl -3-indolylacetic acid, 5-benzoyl -1,2-dihidro -3H-pyrrolo[1,2-a]pyrrole -1-carboxylic acid, 6-methoxy -2-naphthylacetic acid which, according to the present invention, have the following general formula:



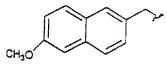
(IA)

where:

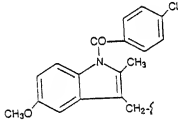
A and B are chosen among hydrogen, linear or branched, substituted or non substituted alkyl chains, M is chosen among:



(XXX)



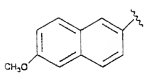
(XXXI)



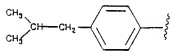
(XXXII)

(XXXIII)

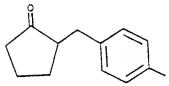
where R is chosen among:



(II)



(III)



(X)

Y is chosen among oxygen, NH, NR_1, where R_1 is a linear or branched alkyl group, and n is comprised between 1 and 10.

More particularly, the fragment

is a linear, branched or cyclic alkylenic group C_2-C_{10}. In fact, it has been observed that the introduction of a group such as a terminal nitric ester in the derivatives (IA) permits to mantain the pharmacological activity which is characteristic of anti-inflammatory non steroidal and/or analgesic agents, leads to products provided with good tolerance, while eliminating the adverse reactions caused by the treatment with such drugs. Furthermore, the introduction of a terminal nitric ester in the derivatives of propionic acid, permits to potentiate the anti-inflammatory effect compared with the well known non-steroidal anti-inflammatory drugs; such increase is made by the terminal nitric ester group, which can be considered as a source of nitric oxide and which can exert additional anti-inflammatory effects.

It has been also observed that the derivatives (IA) are useful in the treatment of different unhealthy conditions, for instance unhealthy conditions which required the treatment with both anti-inflammatory and analgesic drug, or rheumatic diseases in general, disorders of an immunologic nature, and they can also alleviate moderate-medium painful states of any kind.

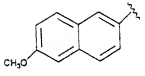
Moreover, the derivatives (IA) subject matter of this invention, are useful in the treatment of the illnesses of the cardiovascular system and of the central nervous system, in particular in the treatment of myocardial and brain ischemiae, as well as in some cases of arterial thrombosis and in some cases of senile dementia.

Always according to this invention, a nitric ester (IA) proved to be particularly advantageous, where:

hydrogen is chosen as A and B, M is chosen as

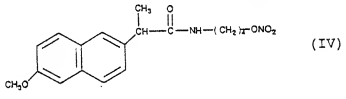
(XXXIII)

where R is chosen as:



(II)

NH is chosen as Y, and n is equal to four, according to the following formula:

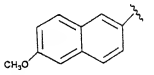


(IV)

A nitric ester (IA) has also proved to be particularly advantageous according to this invention, where: hydrogen is chosen as A and B, M is chosen as

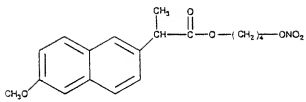
(XXXIII)

where R is chosen as:



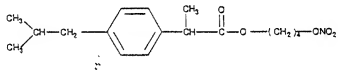
(II)

oxygen is chosen as Y, an n is equal to four, according to the following formula:



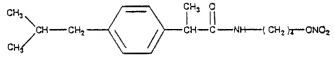
(V)

Also the nitric esters of derivatives of 2-(4-isobutylphenyl)propionic acid have proved to be particularly advantageous according to this invention, having the following formulae:



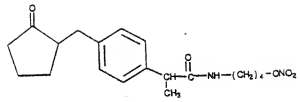
(XIII)

and

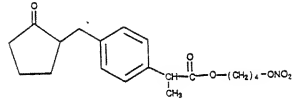


(XIV)

Always according to the present invention, nitric esters (IA) have proved to be particularly advantageous, having the following formulae:

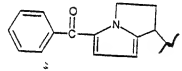


(XI)



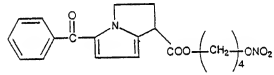
(XII)

Always according to the present invention, nitric esters (IA) where M is chosen as



(XXX)

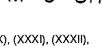
oxygen is chosen as Y, hydrogen is chosen as A and B and n is equal to four according to the following formula:



(XXXIV)

proved to have very good tolerance.

For the preparation of nitric esters (IA) subject matter of the present invention, a first process has proved to be particularly advantageous which, according to the present invention, includes the following steps: - Preparation of sodium salt of derivatives having the following general formula:

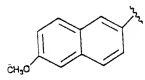


(VIA)

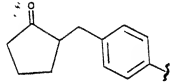
where M is chosen among (XXX), (XXXI), (XXXII),

(XXXIII)

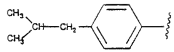
where R is chosen among the following structures:



(II)



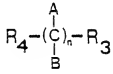
(X)



(III)

or preparation of derivatives (VIA) functionalized to the carboxylic group as acylic chlorides, anhydrides or the like;

- Reaction between the sodium salt of said derivatives (VIA) or of said derivatives (VIA) functionalized to the carboxylic group, with a composition having the following general formula:



(VII)

where:

R_4 is chosen among chlorine, bromine, NHR_5 with R_5 hydrogen, linear or branched alkyl chain, A and B are chosen among hydrogen, linear or branched, substituted or non substitutes alkyl chains, R_3 is chosen among chlorine, bromine and iodine, and n is comprised between 1 and 10, with ensuing production of the relevant monomeric esters or the relevant amides;

- Reaction of said monomeric esters or said amides with a nitrating agent such as $AgNO_3$ or the like, with ensuing production of nitric esters (IA).

A second process has also proved to be particularly advantageous which, always according to the present invention, includes the following steps:

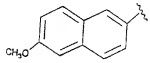
- Preparation of sodium salt of derivatives having the following general formula:

(VIA)

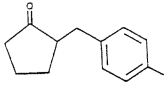
where M is chosen among (XXX), (XXXI), (XXXII),

(XXXIII)

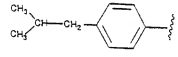
where R is chosen among the following structures:



(II)



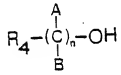
(X)



(III)

or preparation of derivatives (VIA) functionalized to the carboxylic group, such as acylic chlorides, anhydrides or the like;

- Reaction between the sodium salt of said derivatives (VIA) or of said derivatives (VIA) functionalized to the carboxylic group, with a composition having the following general formula:



(VIII)

where;

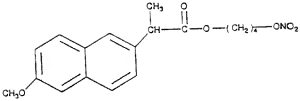
R_4 is chosen among chlorine, bromine, NHR_5 with R_5 hydrogen, linear or branched alkyl chains, A and B are chosen among hydrogen, linear or branched, substituted or non substituted alkyl chains, and n is comprised between 1 and 10, with ensuing production of the relevant monomeric esters or the relevant amides; - Reaction of said monomeric esters or said amides with an halogenating composition such as PBr_3 or the like, with ensuing prouction of said monomeric esters or said amides characterized by the presence of a terminal halogen group;

- Reaction of said monomeric esters or said amides characterized by the presence of a terminal halogen group, with a nitrating agent such as $AgNO_3$ or the like, with ensuing production of nitric esters of derivatives (IA).

The solvents which are utilized in the processes subject matter of the present invention are preferably chosen among chloroform, methylene chloride, acetonitrile, dimethylformamide, tetrahydrofuran, 1,4-dioxane and the like.

Such processes for the preparation of derivatives (IA), subject matter of the present invention, consist of a limited number of steps, which permits to obtain in a short time the products which derive from these processes, with satisfactory yields and in high amounts, also on the industrial level.

According to the processes subject matter of this invention, the preparation of a nitric ester derived from propionic acid has proved to be particularly advantageous, having the following formula:



(V)

which is prepared as described in the example that is given hereunder as a mere indication and which does not limit in any way the protection scope of the invention.

EXAMPLE 1

a) 0.59 g of EtONa dissolved in 10 ml of ethyl alcohol were added, by slow dripping, to a solution of 2 g of 2-(6-methoxy-2-naphtyl)propionic acid, dissolved in 20 ml of ethyl alcohol. The reaction mixture was stirred for 5 minutes at room temperature, then the solvent was evaporated at a reduced pressure, obtaining 2.1 g of sodium salt of 2-(6-methoxy-2-naphtyl)propionic acid.

The 2.1 g of sodium salt of 2-(6-methoxy-2-naphtyl) propionic acid so obtained were disperded in 40 ml of dimethylformamide and 1.5 g of 1-Br-4-Cl-butane dissolved in 30 ml of dimethylformamide were added by dripping to this dispersion. The reaction mixture was stirred for 12 hours at room temperature, then diluted with water and extracted with methylene chloride. The organic phase so extracted was anhydrified on sodium sulfate and the solvent was evaporated at a reduced pressure until a dry residue of 2 g was obtained.

The residue was purified by chromatography on silica gel, utilizing an eluting mixture constituted by hexane/ether 7/3 (v/v).

The head fractions were collected, the solvent was evaporated at a reduced pressure and 1 g of 2-(6-methoxy-2-naphtyl)propionate of 4-chlorobutyl (IX) was obtained.

IR(cm^{-1}):C=0, 1669.

^{1}H-NMR(300MHz) ($CDCl_3$): 1.6ppm (d,3H); 1.75ppm (m, 4H); 3.45ppm (m, 2H); 3.88ppm (q,1H); 3.91ppm (1,3H); 4.1ppm (m, 2H); 7.1-7-7.7ppm (m, aromatics).

Mass spectrometry (i.e.): M^+ • 320.

b) 0.79 g of $AgNO_3$ dissolved in 1.3 ml of acetonitrile were dripped to 1 g of (IX) obtained as described in a), dissolved in 4,5 ml of acetonitrile. The reaction mixture was stirred for 12 hours at a temperature of 85°C and then filtered.

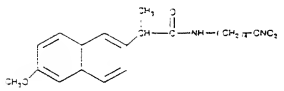
From the resulting solution, the solvent was evaporated at a reduced pressure, and a residue was obtained to which 10 ml of methylene chloride were added. The mix so obtained was filtered once again, the organic phase was washed with water and then anhydrified on sodium sulfate. The solvent was evaporated under reduced pressure and 1.8 g of a dry residue was obtained, which was purified by chromatography on silica gel, utilizing an eluting mixture constituted by hexane/ether 7/3 (v/v). The fractions containing the product were collected, the solvent was evaporated at a reduced pressure and 1.5 g of nitric ester of 2-(6-methoxy-2-naphtyl)propionate of 4-hydroxybutyl (V) were obtained.

IR(cm^{-1}): C=0,1733; ONO_2, 1637.

^{1}H-NMR(300MHz) ($CDCL_3$): 1.6ppm (d,3H); 1.65ppm (m, 4H); 3.8ppm (q, 1H); 3.9ppm (s,3H); 4.1ppm (m, 2H); 4.3ppm (m, 2H); 7.1-7.7ppm (m, aromatics).

Mass spectometry (i.e.) M^+ • 347.

Always according to the processes subject matter of the present invention, also the preparation of a nitric ester derivated from propionic acid proved to be particularly advantageous, having the following formula:



(XV)

which is prepared as described in the following example, that is given hereunder as a mere indication and which does not limit in any way the protection scope of this invention.

EXAMPLE 2

a) 23.9 g of potassium-phtalimide dispersed into 200 ml or anhydrous dimethylformamide were added to a solution of 55.7 g of 1,4-di bromo-butane dissolved in 300 ml of anhydrous dimethylformamide.

The reaction mixture was agitated for 12 hours at room temperature, then diluted with water and extracted with methylene chloride. The methylene chloride was evaporated from the organic phase so obtained at a reduced pressure and then the dimethylformamide was removed by distillation at the pressure of 1.33 KPa (10 mm Hg.)

The residue was regained with water and extracted with methylene chloride.

Tha organic phase so obtained was anhydrified and the solvent was evaporated at a reduced pressure until 14.8 g of 1-phtalimide-4-bromo-butane were obtained, which were treated with isopropyl ether and then essiccated.

m.p. = 77°C

b) 32 ml of hydriodic acid were cautiously added to 8.25 g of 1-phtalimido-4-bromo-butane; the mixture was then submitted to heating and kept in ebullition for 24 hours.

After cooling, the mixture was diluted with water and after filtration the solvent was evaporated at a reduced pressure, obtaining a residue which, once crystallized by ethyl ether, produced 6 g of 4-iodine-butylammonium iodide.

m.p. = 103°C

c) 7 ml of thionyl chloride were cautiously added to a solution of 2.3 g of 2-(6-methoxy-2-naphtyl)propionic acid in 15 ml of anhydrous chloroform. The reaction mixture was stirred for 40 minutes at room temperature and then the solvent was evaporated at a reduced pressure, obtaining 2.23 g of 2-(6-methoxy-2-naphtyl)propionylchloride.

2.3 g od 2-(6-methoxy-2-naphtyl)propionylchloride were dissolved in pyridine and the solution was cooled at the temperature of 0°C.

3.27 g of 4-iodobutylammonium iodide were added to this solution and the mixture so obtained was agitated for 1 hour at 0°C and then diluted with water and extracted with methylene chloride.

The organic phase so obtained was washed initially with a 10% solution of hydrochloric acid and afterward with a saturated solution of sodium bicarbonate, then the solvent was evaporated at a reduced pressure, obtaining 3.2 g of a dry residue. The residue was purified by chromatography on silica gel, utilizing methylene chloride as eluent.

The intermediate fractions were collected, the solvent was evaporated at a reduced pressure and 1.6 g of 2-(6-methoxy-2-naphtyl)-4-iodobutyl propionamide (XX) were obtained.

IR (cm^{-1}): NH, 3294; C=0,1651.

^{1}H-NMR(300MHz) ($CDCl_3$): 1.1-1.75 ppm (m, 4H); 1.6ppm (d, 3H); 3.1ppm (t, 2H); 3.2ppm (q, 2H); 3.7ppm (q, 1H); 3.9ppm (s, 3H); 5.35ppm (m, NH); 7.1-7.75ppm (m, aromatics).

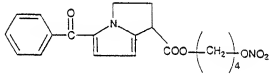
d) A suspension of 1.6 g of 2-(6-methoxy-2-naphtyl)-4-iodobutyl propionamide in 20 ml of acetonitrile was heated at a temperature of about 40°C and stirred until a solution was obtained to which 1.0 g of $AgNO_3$ were added.

The mixture was stirred for 1 hour at room temperature, then filtered and the solvent was evaporated at a reduced pressure. The residue obtained was regained with methylene choride, the resulting mixture was filtered and the solvent was evaporated at a reduced pressure, and 0,8 g of dry residue were obtained which were purified by chromatography on silica gel, utilizing an eluting mixture constituted by methylene chloride/ethyl acetate 9/1 (v/v).

The head fractions were collected, the solvent was evaporated at a reduced pressure and 0.75 g of nitric ester of 2-(6-methoxy-2-naphtyl)-4-hydroxybutyl propionamide (IV) were obtained.

IR(cm^{-1}): C=0,1672; NH, 3294; ONO_2, 1637
Mass spectometry (i.e.) M^+ • 346.
^{1}H-NMR(80mhz) ($CDCl_3$): 1.3ppm-1.6ppm (m, 4H); 1.7ppm (d, 3H); 3.1ppm (q, 2H); 3.7ppm (q, 1H); 3.9ppm (s, 3H); 4.3ppm (m, 2H); 5.6ppm (m, NH); 7.05-7.8ppm (m, aromatics).

Always according to the present invention, also the nitric ester having the following formula:

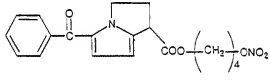


(XXXIV)

proved to be particularly advantageous, which is prepared as described in the following example that is also given hereunder as a mere indication and which does not limit in any way the protection scope of this invention.

EXAMPLE 3

Preparation of the composition having the formula:

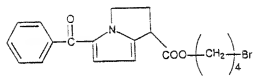


(XXXIV)

a) In a suspension of 80% sodium hydride (0,16 g) in DMF (15 ml), 1,15 g of Ketorolac dissolved in 20 ml of DMF were caused to drip under agitation.

The reaction mix was kept under agitation at 40°C for 15 minutes, then 1 ml of 1,4-dibromobutane was added and the mix was kept under agitation at room temperature overnight.

Then the solvent was evaporated under reduced pressure and the residue was treated with water and methylene chloride. The organic phase was separated, dryed on sodium sulfate and the solvent was removed under reduced pressure, to obtain a residue which was purified by silica gel chromatography, utilizing a 4/6 petroleum ether/ether eluent mix (v/v). The head fractions were collected, the solvent was evaporated under reduced pressure and 0.75 g of product was obtained having the formula:



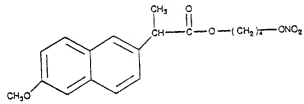
(XXXV)

^{1}H-NMR (80 MHz) ($CDCl_3$) (ppm): 1,83(6H, m); 2,81(2H, m); 3,38(2H, t); 4,12(2H, t); 4,48(1H,m); 6,03(1H, d); 6,78(1H,d); 7,41(3H, m); 7,73(2H, m).

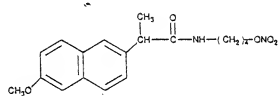
b) A solution of $AgNO_3$ (0,5 g) in 5 ml of acetonitrile was added to a solution of (XXXV) (0,75 g) in 20 ml of acetonitrile. The reaction mix was kept stirring at room temperature for 48 hours. The solvent was then removed under pressure and the residue was treated with water and methylene chloride. The organic phase was then separated, dryed on sodium sulfate and the solvent was removed under reduced pressure. The residue was purified by filtration on silica gel, utilizing a 4/6 petroleum ether/ether eluent mix. The head fractions were collected, the solvent was evaporated under reduced pressure and 0.35 g of (XXXIV) were obtained.

^{1}H-NMR (80 MHz) ($CDCl_3$)(ppm): 1.78(6H, m); 2.82(2H, m); 4.14(2H, m); 4.47(3H, m); 6.03(1H, d); 6.79(1H, d); 7.46(3H, m); 7.77(2H, m).

Through biological assays the anti-inflammatory and analgesic activity were determined, for instance of nitric esters (IA) having the following formulae:



(V)



(IV)

The anti-inflammatory activity of said nitric esters of derivatives of propionic acid was determined in Wistar rats utilizing the method of carrageenan edema, as reported in C.A. WINTER, E. RISLEY, G.W. NUSS, Proc. Soc. Exp. Biol. Med. 111,544-547 (1962), while the analgesic activity of said derivatives was determined in Swiss mice as reported by L.C. HENDERSHOT, J. FORSAITH, J.Pharmacol. Exp. Ter. 125,237-249 (1959).

The anti-inflammatory and analgesic activity of said derivatives resulted to be comparable to 2-(6-methoxy-2-

naphtyl)propionic acid taken as a reference.

The anti-platelet aggregation activity of said derivatives was determined on human platelets. Platelets were incubated with the compounds for 10 min at 37°C prior to stimulation with trombin. The anti-platelet aggregation activity of said derivatives resulted to be comparable to 2-(6-methoxy-2 -naphthyl)propionic acid taken as a reference.

Then, the acute toxicity of said derivatives (IV) and (V) was evaluated by oral administration ot a single dose of each composition (IV) and (V), utilizing groups of 10 Swiss mice for each derivative.

The incidence of lethality and the onset of a toxic symptomatology were reported for an observation period of 14 days.

Even after the administration of a dose of 750 mg/kg of composition (IV) or composition (V) no apparent toxicity simptoms were observed in the treated animals.

Further biological assays were carried out in order to detine the pharmaco-toxicological profile of the studied compounds, in particular of composition (V), compared with 2-(6-methoxy-2-naphtyl)propionic acid taken as reference.

A. PHARMACODYNAMIC ACTIVITY

ACUTE MODELS

Rat carrageenan paw edema. On the basis of preliminary experiments, the compound (V) and 2-(6-methoxy-2-naphtyl)propionic acid prove to have a comparable efficacy; the effective dose is comprised in the range from 1 to 10 mg/kg p.o.

SUBACUTE MODELS

Rat adjuvant arthritis. The animals treated for 19 running days (from the 3rd to the 20th day after the inducing injection) with composition (V) or with 2-(6-methoxy-2-naphtyl)propionic acid, both of them at doses of 3 mg/kg p.o., showed a significant and comparable reduction in arthritic symptomatology compared with controls.

B. GASTROINTESTINAL TOLERABILITY

Damage to the gastric mucosa of the rat. The compound (V) was studied in comparison with 2-(6-methoxy-2-naphtyl)propionic acid taken as reference, both of them at doses comprised between 3 and 30 mg/kg p.o.; the compound (V) proved to be significantly better tolerated than 2-(6-methoxy-2-naphtyl)propionic acid. 2-(6-methoxy-2-naphtyl)propionic acid already at 3 mg/kg caused gastric damages, and such effects resulted to be dose-dependent, while the compound (V) proved to be well tolerated even at doses of 30 mg/kg.

C. GENERAL PHARMACOLOGY

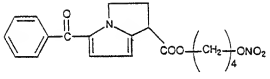
A secondary pharmacological evaluation of compound (V) was carried out in comparison with 2-(6-methoxy-2-naphtyl)propionic acid. No considerable additional effects with respect to the primary pharmacological activity were observed on central nervous system, on the autonomous system, on the cardiovascular, respiratory and gastrointestinal systems.

D. TOXICOLOGY

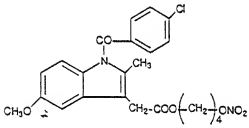
Acute toxicity in rodents. Preliminary studies were carried out in rodents, utilizing two administration routes. No simptoms of apparent toxicity were observed in animals treated with oral or intraperitoneal doses of 300 mg/kg.

Maximum tolerated dose in non-rodents. Preliminary studies have indicated that compound (V) was very well tolerated in the dog, an animal species which is known to be particularly sensitive to the ulcerogenic activity of anti-inflammatory agents in general. The animals received increasing oral doses of compound (V) up to 30 mg/kg and no apparent symptoms were observed. In comparison, 2-(6-methoxy-2-naphtyl)propionic acid, administered at doses ot 10 mg/kg, caused the death of the animals.

Furthermore, biological studies concerning nitric esters (IA) having the following formulae:



(XXXIV)



(XXXVI)

were carried out.

Then the anti-inflammatory activity, the gastrointestinal tolerability and the platelet anti-aggregating activity of the above compositions were determined.

The anti-inflammatory activity was determined by the method of the carrageenan edema in the rat, as described by C.A.WINTER et al. (1962) Proc.Soc.Exp.Biol.Med. 111,544. The gastrointestinal tolerability was evaluated by oral administration in the rat. The platelet anti-aggregating activity was determined on human platelets stimulated by arachidonic acid, according to the method described by V.BERTELE et al. (1983) Science 220, 517.

The results are shown on Table 1 as values concerning the anti-inflammatory, anti-aggregating activity and the gastrointestinal tolerability of the compositions under examination, expressed as a power ratio relatively to the basic product taken as a unity standard.

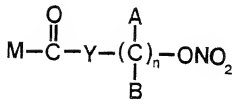
TABLE 1

COMPOSITION	ANTI-INFLAMM. ACTIVITY	ANTI-AGGREG. ACTIVITY	GASTROINTEST. ULCEROGEN.
(XXXIV)	1,25	1,10	0,15
KETOROLAC	1,0	1,0	1,0
(XXXVI)	1,0	1,30	0,1
INDOMETHACIN	1,0	1,0	1,0

The acute toxicity of the compositions under examination has been approximately evaluated by oral administration of a single dosage of the substance to groups of 10 mice. The death-rate incidence and the onset of toxic symptoms have been observed for a period of 14 days. Even after the administration of 100 mg/kg of each composition, the animals did not show any symptom of apparent toxicity.

Claims

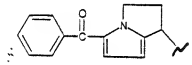
1. Derivatives of propionic acid, 1-(p-chlorobenzoyl) -5- methoxy-2-methyl -3-indolylacetic acid, 5-benzoyl -1,2-dihidro -3H- pyrrolo[1,2-a]pyrrole -1-carboxylic acid, 6-methoxy -2-naphthylacetic acid, characterized in that they have the following general formula:



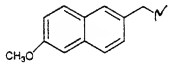
(IA)

where:

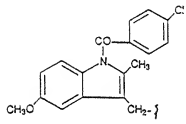
A and B are chosen among hydrogen, linear or branched, substituted or non substituted alkyl chains, M is chosen among:



(XXX)



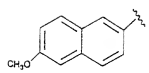
(XXXI)



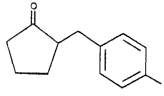
(XXXII)

(XXXIII)

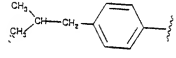
where R is chosen among:



(II)



(X)



(III)

Y is chosen among oxygen, NH, NR_1, where R_1 is a linear or branched alkyl group, and n is comprised between 1 and 10.

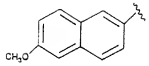
2. Nitric esters according to claim 1, characterized in that the fragment:

is a linear, branched or cyclic alkylenic group C_2-C_{10}.

3. Derivative of propionic acid according to claim 1, characterized in that M is equal to

(XXXIII)

where R is:



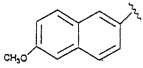
(II)

A and B are equal to hydrogen, Y is equal to oxygen, and n is equal to four.

4. Derivative of propionic acid according to claim 1, characterized in that M is equal to

(XXXIII)

where R is:



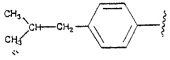
(II)

A and B are equal to hydrogen, Y is equal to NH, and n is equal to four.

5. Derivatives of propionic acid according to claim 1, characterized in that M is equal to

(XXXIII)

where R is equal to:



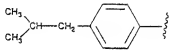
(III)

Y is equal to oxygen, A and B are equal to hydrogen, and n is equal to four.

6. Derivative of propionic acid according to claim 1, characterized in that M is equal to

(XXXIII)

where R is equal to:



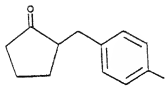
(III)

Y is equal to NH, A and B are equal to hydrogen, and n is equal to four.

7. Derivative of propionic acid, according to claim 1, characterized in that M is equal to

(XXXIII)

where R is equal to



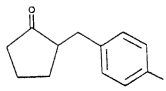
(X)

A and B are equal to hydrogen, y is equal to oxygen and n is equal to four.

8. Derivative of propionic acid according to claim 1, characterized in that M is equal to

(XXXIII)

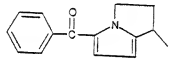
where R is equal to



(X)

A and B are equal to hydrogen, y is equal to NH and n is equal to four.

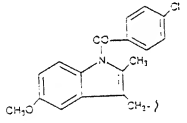
9. Derivatives of 5-benzoyl -1,2-dihydro-3H-pyrrolo[1,2-a] pyrrole -1-carboxylic acid according to claim 1, characterized in that M is equal to



(XXX)

A and B are equal to hydrogen, Y is equal to oxygen and
n is equal to four.

10. Derivatives of 1-(p- chlorobenzoyl) -5-methoxy - 2-methyl-3-indolylacetic acid according to claim 1, characterized in that M is equal to



(XXXII)

A and B are equal to hydrogen, Y is equal to oxygen and
n is equal to four.

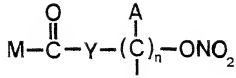
11. Nitric esters according to claim 1 for the use in the pharmaceutical field as anti-inflammatory agents.

12. Nitric esters according to claim 1 for the use in the pharmaceutical field as analgesic agents.

13. Nitric esters according to claim 1 for the use in the treatment of rheumatic illnesses, in the treatment of disorders of an immunologic nature and of the moderate to medium painful states.

14. Nitric esters according to claim 1 for the use in the treatment of the diseases of the cardiovascular system, in the treatment of senile dementia, in the treatment of miocardial and brain ischemiae and in cases of arterial thrombosis.

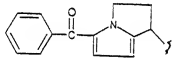
15. Process for the preparation of nitric esters according to claim 1 and having the following general formula:



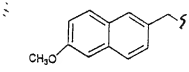
(IA)

where A and B are chosen among hydrogen, linear or branched, substituted or non substituted alkyl chains,

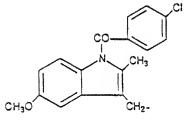
M is chosen among



(XXX)



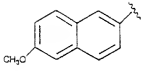
(XXXI)



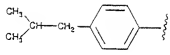
(XXXII)

(XXXIII)

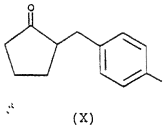
where R is chosen among:



(II)



(III)



(X)

Y is chosen among oxygen, NH, NR_1, where R_1 is a linear or branched alkyl group, and n is comprised between 1 and 10, characterized in that it comprises the following steps:

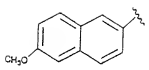
- Preparation of sodium salt of derivatives having the following general formula:

(VIA)

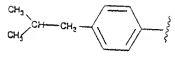
where M is chosen among (XXX), (XXXI), (XXXII),

(XXXIII)

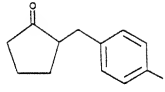
where R is chosen among the following structures:



(II)



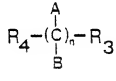
(III)



(X)

or preparation of derivatives (VIA) functionalized to the carboxylic group, such as acylic chlorides, anhydrides or the like;

- Reaction bn between the sodium salt of said derivatives (VIA) or of said derivatives (VIA) functionalized to the carboxylic group, with a compound having the following general formula:



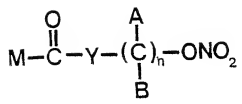
(VII)

where:

R_4 is chosen among chlorine, bromine, NHR_5 with R_5 hydrogen, linear or branched alkyl chain, A and B are chosen among hydrogen, linear or branched, substituted or non substituted alkyl chains, R_3 is chosen among chlorine, bromine and iodine, and n is comprised between 1 and 10, with ensuing production of the relevant monomeric esters or the relevant amides;

- Reaction of said monomeric esters or said amides with a nitrating agent such as $AgNO_3$ or the like, with ensuing production of nitric esters (IA).

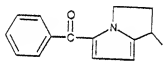
16. Process for the preparation of nitric esters according to claim 1 and having the following general formula:



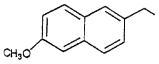
(IA)

where:

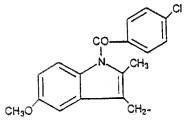
A and B are chosen among hydrogen, linear or branched, substituted or non substitured alkyl chains, M is chosen among



(XXX)



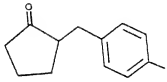
(XXXI)



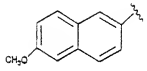
(XXXII)

(XXXIII)

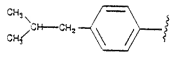
where R is chosen among:



(X)



(II)



(III)

Y is chosen among oxygen, NH, NR_1, where R_1 is a linear or branched alkyl group, and n is comprised between 1 and 10, characterized in that it comprises the following steps:

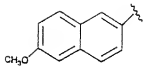
- Preparation of sodium salt of derivatives having the following general formula:

(VIA)

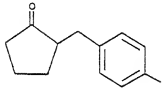
where M is chosen among (XXX), (XXXI), (XXXII),

(XXXIII)

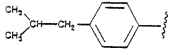
where R is chosen among the following structures:



(II)



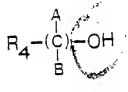
(X)



(III)

or preparation of derivatvatives (VIA) functionalized to the carboxylic group, such as acylic chorides, anhydrides or the like;

- Reaction between the sodium salt of said derivatives (VIA) or of said derivatives (VIA) functionalized to to the carboxylic group, with a composition having the following genernral formula:



(VIII)

where:

R_4 is chosen en among chlorine, bromine, NHR_5 with R_5 hydrogen, linear or branched alkyl chain, A and B are chosen among hydrogen, linear or branched, substituted or non substituted alkyl chains, and n is comprised between 1 and 10, with ensuing production of the relevant mo monomeric esters or the relevant amides;

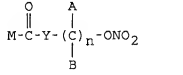
- Reaction of said monomeric esters or said amides with an halogenating compound such as PBr_3 or the like, with ensuing production of said monomeric esters or said amides, characterized by the presence of a terminal halogen group;
- Reaction of said monomeric esters or of said amides, characterized by the presence of a terminal halogen group with a nitrating agent such as $AgNo_3$ or the like, with ensuing production of nitric esters (IA).

17. Pharmaceutical compositions having anti-inflammatory activity characterized in that they comprise at least one nitric ester according to claim 1 as active constituent.

18. Pharmaceutical compositions having analgesic activity characterized in that they comprise at least one nitric ester according to claim 1 as active constituent.

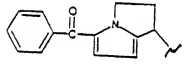
Patentansprüche

1. Derivate von Propionsäure, 1-(p-Chlorbenzoyl)-5-methoxy-2-methyl-3-indolylessigsäure, 5-Benzoyl-1,2-dihydro-3H-pyrrolo[1,2-a]pyrrol-1-carbonsäure, 6-Methoxy-2-naphthylessigsäure, dadurch gekennzeichnet, daß sie die nachstehende allgemeine Formel aufweisen:

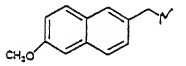


(IA)

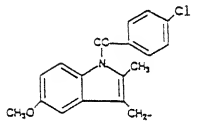
worin A und B ausgewählt sind aus Wasserstoff, linearen oder verzweigten, substituierten oder nichtsubstituierten Alkylketten, M ausgewählt ist aus:



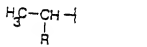
(XXX)



(XXXI)

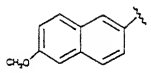


(XXXII)

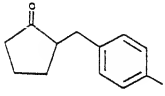


(XXXIII)

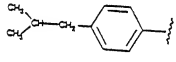
worin R ausgewählt ist aus:



(II)



(X)



(III)

Y ausgewählt ist aus Sauerstoff, NH, NR_1, worin R_1 eine lineare oder verzweigte Alkylgruppe darstellt und n zwischen 1 und 10 umfaßt ist.

2. Salpetersäureester nach Anspruch 1, dadurch gekennzeichnet, daß das Fragment:

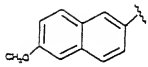
eine lineare, verzweigte oder cyclische C_2-C_{10}-Alkylengruppe darstellt.

3. Derivat von Propionsäure nach Anspruch 1, dadurch gekennzeichnet, daß M

(XXXIII)

ist,

worin R



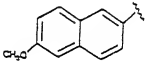
(II)

darstellt,
A und B Wasserstoff sind, Y Sauerstoff ist und n vier ist.

4. Derivat von Propionsäure nach Anspruch 1, dadurch gekennzeichnet, daß M

(XXXIII)

ist, worin R



(II)

darstellt,
A und B Wasserstoff sind, Y NH ist und n vier ist.

5. Derivate von Propionsäure nach Anspruch 1, dadurch gekennzeichnet, daß M

(XXXIII)

ist,

worin R

(III)

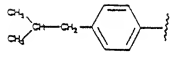
ist,
Y Sauerstoff ist, A und B Wasserstoff sind und n vier ist.

6. Derivat von Propionsäure nach Anspruch 1, dadurch gekennzeichnet, daß M

(XXXIII)

ist,

worin R



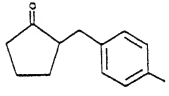
(III)

ist,
Y NH ist, A und B Wasserstoff sind und n vier ist.

7. Derivat von Propionsäure nach Anspruch 1, dadurch gekennzeichnet, daß M

(XXXIII)

ist, worin R



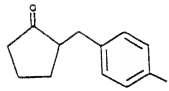
(X)

ist, A und B Wasserstoff sind, Y Sauerstoff ist und n vier ist.

8. Derivat von Propionsäure nach Anspruch 1, dadurch gekennzeichnet, daß M

(XXXIII)

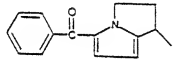
ist, worin R



(X)

ist, A und B Wasserstoff sind, Y gleich NH ist und n vier ist.

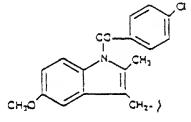
9. Derivate von 5-Benzoyl-1,2-dihydro-3H-pyrrolo[1,2-a]pyrrol-1-carbonsäure nach Anspruch 1, dadurch gekennzeichnet, daß M



(XXX)

ist, A und B Wasserstoff sind, Y Sauerstoff ist und n vier ist.

10. Derivate von 1-(p-Chlorbenzoyl)-5-methoxy-2-methyl-3-indolylessigsäure nach Anspruch 1, dadurch gekennzeichnet, daß M



(XXXII)

ist, A und B Wasserstoff sind, Y Sauerstoff ist und n vier ist.

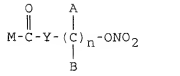
11. Salpetersäureester nach Anspruch 1 zur Verwendung auf dem Arzneimittelgebiet als entzündungshemmende Mittel.

12. Salpetersäureester nach Anspruch 1 zur Verwendung auf dem Arzneimittelgebiet als analgetische Mittel.

13. Salpetersäureester nach Anspruch 1 zur Verwendung bei der Behandlung von rheumatischen Erkrankungen, bei der Behandlung von Erkrankungen immunologischer Natur und von mäßigen bis mittleren Schmerzzuständen.

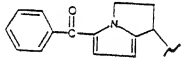
14. Salpetersäureester nach Anspruch 1 zur Verwendung bei der Behandlung von Erkrankungen des cardiovaskulären Systems, bei der Behandlung von seniler Demenz, bei der Behandlung von myocardialer und Hirnischämie und in Fällen von arterieller Thrombose.

15. Verfahren zur Herstellung von Salpetersäureestern nach Anspruch 1 der nachstehenden allgemeinen Formel:

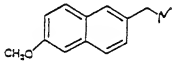


(IA)

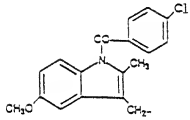
worin A und B ausgewählt sind aus Wasserstoff, linearen oder verzweigten, substituierten oder nichtsubstituierten Alkylketten, M ausgewählt ist aus:



(XXX)



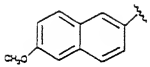
(XXXI)



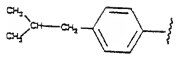
(XXXII)

(XXXIII)

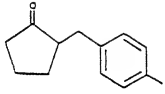
worin R ausgewählt ist aus:



(II)



(III)



(X)

Y ausgewählt ist aus Sauerstoff, NH, NR_1, worin R_1 eine lineare oder verzweigte Alkylgruppe darstellt und n zwischen 1 und 10 umfaßt ist, dadurch gekennzeichnet, daß es die nachstehenden Schritte umfaßt:

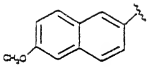
- Herstellung des Natriumsalzes von Derivaten der nachstehenden allgemeinen Formel:

(VIA),

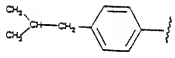
worin M ausgewählt ist aus (XXX), (XXXI), (XXXII),

(XXXIII)

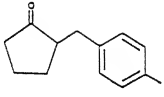
worin R ausgewählt ist aus den nachstehenden Strukturen:



(II)



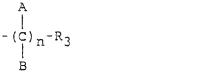
(III)



(X)

oder Herstellung von Derivaten (VIA), die an der Carboxylgruppe funktionalisiert sind, wie Acylchloride, Anhydride oder dergleichen;

- Reaktion zwischen dem Natriumsalz der Derivate (VIA) oder der Derivate (VIA), die an der Carboxylgruppe funktionalisiert sind, mit einer Verbindung der nachstehenden allgemeinen Formel:



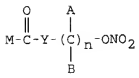
(VII),

worin:

R_4 ausgewählt ist aus Chlor, Brom, NHR_5, wobei R_5 Wasserstoff, eine lineare oder verzweigte Alkylkette darstellt, A und B ausgewählt sind aus Wasserstoff, linearen oder verzweigten, substituierten oder nichtsubstituierten Alkylketten, R_3 ausgewählt ist aus Chlor, Brom und Jod und n zwischen 1 und 10 umfaßt ist, unter anschließender Herstellung der relevanten Monomerester oder relevanten Amide;

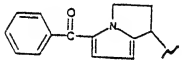
- Reaktion der Monomerester oder der Amide mit einem Nitrierungsmittel, wie $AgNO_3$ oder dergleichen, mit anschließender Herstellung der Salpetersäureester (IA).

16. Verfahren zur Herstellung von Salpetersäureestern nach Anspruch 1 der nachstehenden allgemeinen Formel:

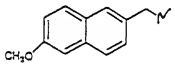


(IA)

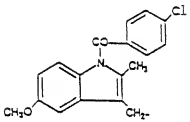
worin A und B ausgewählt sind aus Wasserstoff, linearen oder verzweigten, substituierten oder nichtsubstituierten Alkylketten, M ausgewählt ist aus:



(XXX)



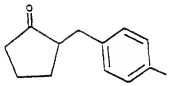
(XXXI)



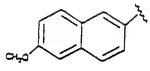
(XXXII)

(XXXIII)

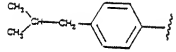
worin R ausgewählt ist aus:



(X)



(II)



(III)

Y ausgewählt ist aus Sauerstoff, NH, NR_1, worin R_1 eine lineare oder verzweigte Alkylgruppe darstellt und n zwischen 1 und 10 umfaßt ist, dadurch gekennzeichnet, daß es die nachstehenden Schritte umfaßt:

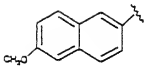
- Herstellung des Natriumsalzes von Derivaten mit der allgemeinen Formel:

(VIA),

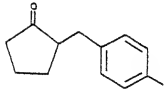
worin M ausgewählt ist aus (XXX), (XXXI), (XXXII),

(XXXIII)

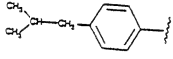
worin R ausgewählt ist aus den nachstehenden Strukturen:



(II)



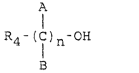
(X)



(III)

oder Herstellung von Derivaten (VIA), die an der Carboxylgruppe funktionalisiert sind, wie Acylchloride, Anhydride oder dergleichen;

- Reaktion zwischen dem Natriumsalz der Derivate (VIA) oder der Derivate (VIA), die an der Carboxylgruppe funktionalisiert sind, mit einer Verbindung der allgemeinen Formel:



(VIII),

worin:

R_4 ausgewählt ist aus Chlor, Brom, NHR_5, wobei R_5 Wasserstoff, eine lineare oder verzweigte Alkylkette darstellt, A und B ausgewählt sind aus Wasserstoff, linearen oder verzweigten, substituierten oder nichtsubstituierten Alkylketten und n zwischen 1 und 10 umfaßt ist, unter anschließender Herstellung der relevanten Monomerester oder relevanten Amide;

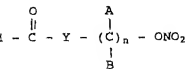
- Reaktion der Monomerester oder der Amide mit einer Halogenierungsverbindung, wie PBr_3 oder dergleichen, unter anschließender Herstellung der Monomerester oder der Amide, gekennzeichnet durch die Gegenwart einer endständigen Halogengruppe;
- Reaktion der Monomerester oder der Amide, gekennzeichnet durch die Gegenwart einer endständigen Halogengruppe mit einem Nitrierungsmittel, wie $AgNO_3$ oder dergleichen, unter anschließender Herstellung von Salpetersäureestern (IA).

17. Pharmazeutische Zusammensetzungen mit entzündungshemmender Wirkung, dadurch gekennzeichnet, daß sie mindestens einen Salpetersäureester nach Anspruch 1 als aktiven Bestandteil umfassen.

18. Pharmazeutische Zusammensetzungen mit analgetischer Wirkung, dadurch gekennzeichnet, daß sie mindestens einen Salpetersäureester nach Anspruch 1 als aktiven Bestandteil umfassen.

Revendications

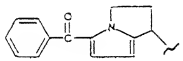
1. Dérivés de l'acide propionique, de l'acide 1-(p-chlorobenzoyl)-5-méthoxy-2-méthyl-3-indolylacétique, de l'acide 5-benzoyl-1,2-dihydro-3H-pyrrolo[1,2-a]pyrrole-1-carboxylique, de l'acide 6-méthoxy-2-naphtylacétique, caractérisés en ce qu'ils ont la formule générale suivante:



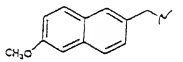
(IA)

dans laquelle

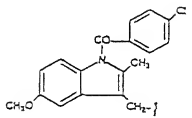
A et B sont choisis parmi l'atome d'hydrogène, les groupes alkyle à chaîne droite ou ramifiée, substitués ou non substitués, M est choisi parmi :



(XXX)



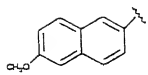
(XXXI)



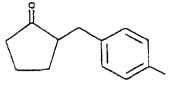
(XXXII)

(XXXIII)

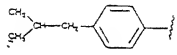
où R est choisi parmi :



(II)



(X)



(III)

Y est choisi parmi l'atome d'oxygène, NH, NR_1, où R_1 est un groupe alkyle à chaîne droite ou ramifiée, et n est compris entre 1 et 10.

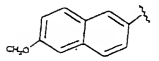
2. Esters nitriques selon la revendication 1, caractérisés en ce que le fragment

est un groupe alkylénique en C_2 à C_{10}, à chaîne droite ou ramifiée, ou cyclique.

3. Dérivé de l'acide propionique selon la revendication 1, caractérisé en ce que M est :

(XXXIII)

où R est :



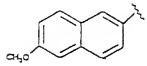
(II)

A et B sont des atomes d'hydrogène, Y est un atome d'oxygène, et n vaut quatre.

4. Dérivé de l'acide propionique selon la revendication 1, caractérisé en ce que M est :

(XXXIII)

où R est :



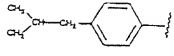
(II)

A et B sont des atomes d'hydrogène, Y est NH, et n vaut quatre.

5. Dérivés de l'acide propionique selon la revendication 1, caractérisé en ce que M est :

(XXXIII)

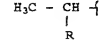
où R est :



(III)

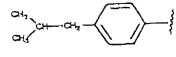
Y est un atome d'oxygène, A et B sont des atomes d'hydrogène, et n vaut quatre.

6. Dérivé de l'acide propionique selon la revendication 1, caractérisé en ce que M est :



(XXXIII)

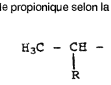
où R est :



(III)

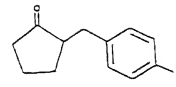
Y est NH, A et B sont des atomes d'hydrogène, et n vaut quatre.

7. Dérivé de l'acide propionique selon la revendication 1, caractérisé en ce que M est :



(XXXIII)

où R est :



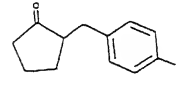
(X)

A et B sont des atomes d'hydrogène, Y est un atome d'oxygène, et n vaut quatre.

8. Dérivé de l'acide propionique selon la revendication 1, caractérisé en ce que M est :

(XXXIII)

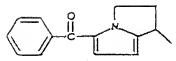
où R est :



(X)

A et B sont des atomes d'hydrogène, Y est NH, et n vaut quatre.

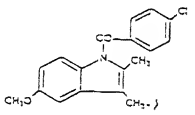
9. Dérivés de l'acide 5-benzoyl-1,2-dihydro-3H-pyrrolo [1,2-a]pyrrole-1-carboxylique selon la revendication 1, caractérisé en ce que M est :



(XXX)

A et B sont des atomes d'hydrogène, Y est un atome d'oxygène, et n vaut quatre.

10. Dérivés de l'acide 1-(p-chlorobenzoyl)-5-méthoxy-2-méthyl-3-indolylacétique selon la revendication 1, caractérisés en ce que M est :



(XXXII)

A et B sont des atomes d'hydrogène, Y est un atome d'oxygène, et n vaut quatre.

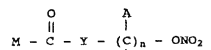
11. Esters nitriques selon la revendication 1, pour utilisation dans le domaine pharmaceutique en tant qu'agents anti-inflammatories.

12. Esters nitriques selon la revendication 1, pour utilisation dans le domaine pharmaceutique en tant qu'agents analgésiques.

13. Esters nitriques selon la revendication 1, pour utilisation dans le traitement des maladies rhumatismales, dans le traitement des troubles de nature immunologique et des états douloureux modérés à moyens.

14. Esters nitriques selon la revendication 1, pour utilisation dans le traitement des maladies du système cardio-vasculaire, dans le traitement de la démence sénile, dans le traitement de l'ischémie myocardique et cérébrale et dans les cas de thrombose artérielle.

15. Procédé pour la préparation d'esters nitriques selon la revendication 1 et ayant la formule générale suivante :

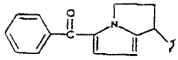


(IA)

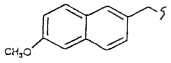
dans laquelle

A et B sont choisis parmi l'atome d'hydrogène et les groupes alkyle à chaîne droite ou ramifiée, substitués ou non substitués,

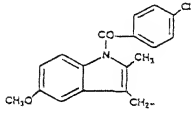
M est choisi parmi :



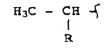
(XXX)



(XXXI)

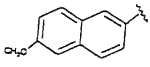


(XXXII)

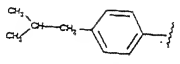


(XXXIII)

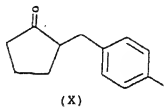
où R est choisi parmi :



(II)



(III)



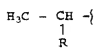
(X)

Y est choisi parmi l'atome d'oxygène, NH, NR_1, où R_1 est un groupe alkyle à chaîne droite ou ramifiée, et n est compris entre 1 et 10, caractérisé en ce qu'il comprend les étapes suivantes :

- Préparation du sel de sodium de dérivés ayant la formule générale suivante :

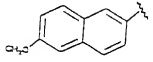
(VIA)

dans laquelle M est choisi parmi (XXX), (XXXI), (XXXII),

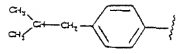


(XXXIII)

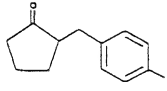
où R est choisi parmi les structures suivantes :



(II)



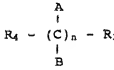
(III)



(X)

ou préparation de dérivés (VIA) fonctionnalisés sur le groupe carboxylique, tels que les chlorures d'acyle, les anhydrides d'acides ou analogues ;

- Réaction entre le sel de sodium desdits dérivés (VIA) ou desdits dérivés (VIA) fonctionnalisés sur le groupe carboxylique, avec un composé ayant la formule générale suivante :

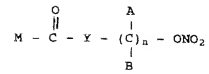


(VII)

dans laquelle R_4 est choisi parmi le chlore, le brome, NHR_5, R_5 étant un atome d'hydrogène ou un groupe alkyle à chaîne droite ou ramifiée, A et B sont choisis parmi l'atome d'hydrogène, les groupes alkyle à chaîne droite ou ramifiée, substitués ou non substitués, R_3 est choisi parmi le chlore, le brome et l'iode, et n est compris entre 1 et 10, avec production ultérieure des esters monomères correspondants ou des amides correspondants ;

- Réaction desdits esters monomères ou desdits amides avec un agent de nitration tel qu'$AgNO_3$ ou analogues, avec production ultérieure d'esters nitriques (IA).

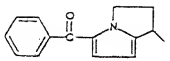
16. Procédé pour la préparation d'esters nitriques selon la revendication 1 et ayant la formule générale suivante :



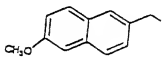
(IA)

dans laquelle

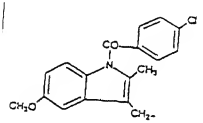
A et B sont choisis parmi l'atome d'hydrogène et les groupes alkyle à chaîne droite ou ramifiée, substitués ou non substitués,
M est choisi parmi :



(XXX)



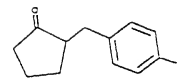
(XXXI)



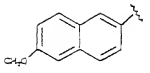
(XXXII)

(XXXIII)

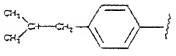
où R est choisi parmi :



(X)



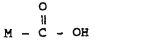
(II)



(III)

Y est choisi parmi l'atome d'oxygène, NH, NR_1, où R_1 est un groupe alkyle à chaîne droite ou ramifiée, et n est compris entre 1 et 10, caractérisé en ce qu'il comprend les étapes suivantes :

- Préparation du sel de sodium de dérivés ayant la formule générale suivante :

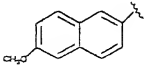


(VIA)

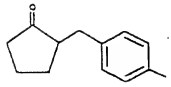
dans laquelle M est choisi parmi (XXX), (XXXI), (XXXII),

(XXXIII)

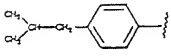
où R est choisi parmi les structures suivantes :



(II)



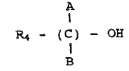
(X)



(III)

ou préparation de dérivés (VIA) fonctionnalisés sur le groupe carboxylique, tels que les chlorures d'acyle, les anhydrides d'acides ou analogues ;

- Réaction entre le sel de sodium desdits dérivés (VIA) ou desdits dérivés (VIA) fonctionnalisés sur le groupe carboxylique, avec une composition ayant la formule générale suivante :



(VIII)

dans laquelle

R_4 est choisi parmi le chlore, le brome, NHR_5, R_5 étant un atome d'hydrogène ou un groupe alkyle à chaîne droite ou ramifiée, A et B sont choisis parmi l'atome d'hydrogène et les groupes alkyle à chaîne droite ou ramifiée substitués ou non substitués, et n est compris entre 1 et 10, avec production ultérieure des esters monomères correspondants ou des amides correspondants ;

- Réaction desdits esters monomères ou desdits amides avec un composé d'halogénation tel que PBr_3 ou analogues, avec production ultérieure desdits esters monomères ou desdits amides, caractérisé par la présence d'un groupe halogéno terminal ;
- Réaction desdits esters monomères ou desdits amides, caractérisés par la présence d'un groupe halogéno terminal, avec un agent de nitration tel qu'$AgNO_3$ ou analogues, avec production ultérieure d'esters nitriques (IA).

17. Compositions pharmaceutiques ayant une activité anti-inflammatoire, caractérisées en ce qu'elles comprennent au moins un ester nitrique selon la revendication 1 en tant que principe actif.

18. Compositions pharmaceutiques ayant une activité analgésique, caractérisées en ce qu'elles comprennent au moins un ester nitrique selon la revendication 1 en tant que principe actif.